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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/524,454	03/10/2000	Kristian Berg	697.013US1	5804

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/15/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com

Office Action Summary	Application No.	Applicant(s)	
	09/524,454	BERG ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,8-10 and 24-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,8-10 and 24-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 5/04/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment, remarks, and IDS filed 5/04/09 have been entered.

2. Claims 2, 4, 8-10, 24-38, and newly added Claims 39 and 40 are pending and being acted being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2, 4, 8-10, 24-38, and newly added Claims 39 and 40 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used for expressing a molecule on a cell, said method comprising photochemical internalization wherein the molecule is sufficient to generate an immune response (e.g., Claim 24), more specifically CTL mediated cell killing (e.g., Claim 2), for the reasons of record. Additionally, the specification provides insufficient evidence that the claimed method could be used for the limitations of Claim 37 wherein the peptide and photosensitizing agents employed in the claimed method are administered directly to a patient.

As set forth previously, the breadth of the claims, in light of the limited disclosure of the specification, would not allow one of skill in the art to practice the invention as broadly claimed without an undue amount of experimentation.

First note that it is clear that the photochemical method (employing certain disclosed agents) of the instant application (and the prior art) can be used to internalize exogenous molecules. The method of the instant claims, however, requires more. The claimed method requires the surface presentation of a sufficient amount of the internalized molecule to generate an immune response.

It is well-known in the immunological arts that only certain antigen presenting cells are capable of presenting antigens and generating an immune response. See, for example, Janeway et al. (1994) wherein it is taught that in addition to antigen presentation, costimulation that can only be provided by B cells, macrophages, or dendritic cells, is required for the generation of an immune response. Accordingly, it appears that the method of Claims 2-5 and 7-11, employing any cell capable of photochemical internalization, could not be performed without an undue amount of experimentation.

Further regarding the breadth of the claims, the specification discloses only the actual use of $AlPcS_{2a}$ and $TPPS_{2a}$ as photochemical internalization agents. Claims 2-7 and 9-11 comprise either no limitations regarding photochemical internalization agents, or as in the case of Claim 7, are drawn to whole classes of agents. The disclosure of two related species of agents cannot be considered to be reasonably sufficient to enable the method of the instant claims to be performed with any of the essentially unlimited number of disclosed families of chemicals without an undue amount of experimentation.

Finally, it remains the Examiner's position that the disclosure of the specification does not sufficiently demonstrate the required limitation that the claimed method be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response. As set forth previously, the specification fails to disclose any actual Class I MHC presentation. Indeed, the only experiment which might demonstrate any sort of surface presentation, Example 3, clearly demonstrates the opposite, the triangles of Figure 4 show a *lack* of antigen on the surface of the cells.

Example 2 was discussed in the Office action of 1/09/07. Regarding Example 2, said example was discussed in the actions of 4/01/05 and 11/29/05:

In regards to Example 2, the methods of the example are not the methods of the instant claims, nor are they representative of the scope of the methods of the instant claims. In the example, a single cell type is loaded with a particular antigen; said loaded cell is then used in a CTL ^{51}Cr release assay. The CTLs employed in a ^{51}Cr assay are primed/activated CTLs and are not representative of the generation or stimulation of an immune response, i.e., the method of the instant claims. See, for example, Janeway et al. (1994) wherein one of the fundamental rules of cellular immunology is taught, i.e., that the generation of an immune response from naïve T cells *requires* professional APCs. Clearly then, the ^{51}Cr assay of Example 2 employs primed/activated CTLs and does not comprise the generation or stimulation of an immune response. Note also that the specification discloses that the assay of Example 2 is the assay of Fossum et al. (1995) in which primed CTLs were employed. Accordingly, it remains the Examiner's position that given the breadth of the claimed method, i.e., the employment of *any*

cell type in the production of cells capable of generating an immune response (in defiance of one of the fundamental concepts of cellular immunology), the specification provides insufficient support and is not enabling. Further, because the example comprises no appropriate controls, the skilled artisan would know that no conclusions could be drawn based on the disclosed results.

Applicant's arguments, filed 5/04/09 have been fully considered but they are not persuasive. Applicant argues that the Examiner alleges that the specification does not enable the claimed method of expressing a molecule on a cell.

The rejection is actually based on a lack of enablement in stimulating an immune response as is broadly claimed. While it is inherent that a MHC class I-restricted memory response could be induced under the right conditions, there is no evidence of record that either a primary (naive) MHC class I-restricted immune response (CTL), nor any sort of MHC class II-restricted immune response could be induced or generated.

Applicant argues that Example 2 enables the claimed method.

Example 2 has been discussed repeatedly over the 7.5 year course of prosecution in this application (beginning in the first action rejections of 4/24/01). Simply put, the Example is not representative of the scope of the method as is broadly claimed. As set forth previously, the Example comprises merely the simplest and most easily induced type of immune response (memory) and it cannot enable the broadly claimed response that encompasses the activation of a naive cytotoxic T cell (CTL) response as well as the induction of said response by cells other than antigen presenting cells (in certain claims). Nor can the example enable a MHC class II-restricted immune response. Particularly note page 9 of the specification wherein it is disclosed that, "The term "stimulating an immune response" thus includes all types of immune responses and mechanisms for stimulating them," as a demonstration of how broad the claimed method is reasonably intended to be viewed.

Applicant cites Ditzel et al. (1993, IDS).

Applicant's interpretation of the teachings of the reference is nonsensical. There is no teaching in the reference regarding how the lymphocytes from a rectal cancer patient that produced the antibody used in the reference were generated. Applicant's assertion that, "the Ditzel antibody was originally generated against cancer antigens that are cell-bound, i.e., the

cancer cells presented the antigen," is not supported by the reference nor an understanding of immunology. Most likely the antigen to which the antibody binds was scavenged from some source and originally presented by some form on some pAPC.

Applicant again cites the 11/13/02 declaration of Inventor Hogset.

As set forth previously, the declaration of Inventor Hogset was considered in the Office action of 2/10/03:

In regards to the 1.132. declaration of Inventor Hogset, it is now disclosed that factors not disclosed in the specification are critical to the functionality of the claimed method. "Whether or not cell death results after photochemical treatment is principally dependent on two factors. Firstly the amount of toxic substances generated by the photosensitizing compounds on exposure to light and secondly, the presence and toxicity of molecules which are internalized during this process." Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation in view of these newly disclosed factors.

Regarding the photosensitizing compounds and exposure to light, while specific photosensitizing compounds are disclosed and claimed, no specific concentrations of said photosensitizing compounds (other than that used in Example 2) are claimed nor disclosed. Clearly, this parameter must be considered in that too much photosensitizing agent will induce cell death. Even more importantly, the declaration discloses that, whereas "the level of toxic substances which are generated may be controlled by the selection of the photosensitizer to be used, [and] the dose of that photosensitizer, but most crucially, the time of illumination which leads to increasing levels of the toxic substances" [must be considered]. The declaration goes on to demonstrate that too little light will not induce internalization while too much light kills the cells. Again it is clear, particularly in regards to the light parameters, i.e., source (wavelength), intensity, and duration, that the specification provides insufficient support for the claimed method. Again, given the lack of guidance in the specification, the claimed method must then be considered highly unpredictable and requiring of undue experimentation.

Finally, regarding the antigen to be internalized, the instant declaration states "the toxicity resulting from the molecules which are introduced may be readily controlled by selecting an appropriate toxic or non-toxic molecule for transfer, depending on the desired end use." The specification discloses however, that essentially any antigen can be used including "all manner" of pathogenic antigens, as well as peptides involved in diseases ranging from cancer to multiple sclerosis. The specification fails, however, to disclose how to "appropriately select" among the toxic and non-toxic molecules. Indeed, even the instant post-filing declaration fails to indicate how such a selection is to be made; it only indicates that said selection is essential, which once again demonstrates the lack of guidance in the specification.

Regarding toxicity, the specification fails to even mention this possible problem. Said problem was brought to light only in the Inventor's own post-filing declaration. Clearly then, the specification cannot be enabling in this regard.

Applicant cites U.S. Patent No. 7,223,600 and Berg et al. (1999, IDS) in support of the enablement of the use of generic photochemical internalizing agents.

A review of both documents shows only the actual use of a very limited number of photochemical internalizing agents (essentially the same agents used in the instant specification). Neither document shows the use of generic porphyrins, chlorins, nor phthalocyanines as claimed (e.g., Claim 2).

Applicant notes that the language containing the term "MHC class I molecules" has been deleted from the claims.

Said deletion is noted, though the term is still found in Claim 24. It is still noted, however, that both MHC class I and class II antigen presentation would be required for the method as claimed to function as broadly claimed.

Applicant cites Example 3.

Example 3 has been addressed previously. The example shows what it shows - cytosolic localization of antigen and very low surface presentation of antigen. While Applicant speculates that the antigen is broken up and little of its visualizing activity is seen on the surface of the cell, there is no evidence of this and the argument alone is not persuasive.

Applicant argues that the claims are not directed to the use of any cell types, in particular Claim 2 is limited to the use of cancer cells and Claims 24 and 38 are limited to the use of antigen presenting cells.

It is unlikely that a cancer cell, except for a transformed antigen presenting cell, would be able to induce a primary immune response nor any sort of MHC class II-mediated immune response. Indeed, the *only* type of immune response that a cancer cell would be expected to induce would be a MHC class I-mediated memory response, e.g., as exemplified in Example 2. As set forth repeatedly through the course of the prosecution of this application, this is just one simple type of immune response, and the claims are not even limited to this type of immune response. Even regarding the APCs of Claims 24 and 38, given a lack of definition of APCs in the specification, but a broad teaching as set forth in the paragraph spanning pages 8 and 9 of the specification that the APCs of the claims are,

"involved in any aspect or "arm" of the immune response", it is not unreasonable to assume that Applicant is intending to encompass the use of any cell capable of MHC class I antigen presentation, i.e., essentially all cell types except red blood cells.

Finally note that given the fundamental difference between a MHC class I and MHC class II immune response, and in particular the source of the antigen presented (the cytosol for class I and intracellular vesicles for class II), there is no evidence of record to support the generation of a class II response by the claimed method even employing a pAPC. It is well established that cytosolic antigens are processed and presented only through the MHC class I pathway thus, a class II immune response would not be possible.

As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC, 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir., 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, and the lack of sufficient working examples encompassing the broadly claimed method, it would take undue trials and errors to practice the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 2, 4, 8-10, 28-37, and newly added Claims 39 and 40 stand/are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/07432 (IDS).

As set forth previously, WO96/07432 teaches a method of expressing [now presenting an antigenic molecule on the surface of a viable cancer cell, said method comprising:

contacting said cell *in vitro* [and *ex vivo*] with said antigenic molecule [now peptide] (including a vaccine component, a molecule capable of stimulating an immune response, and a peptide, also including an antigen bound to a carrier molecule) and with a photosensitizing agent (a porphyrin, phthalocyanine, purpurin, chlorin, benzoporphyrin, naphthalocyanine, cationic dye, and tetracycline, including $TPPS_4$, $TPPS_{2a}$, and $AlPcS_{2a}$, also including a photosensitizing agent bound to a carrier molecule), wherein said molecule and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; and irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said molecule into the cytosol of the cell, without killing the cell by irradiation, wherein, said released antigenic molecule, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I MHC molecule (see particularly the claims). Note that reference does not specifically state that the method results in the cell surface expression of the antigen in MHC Class I, however, the reference teaches the same steps as those of the instant claims, thus, said same steps would inherently result in the same outcome, i.e., the claimed method of the expressing an antigenic molecule on the surface of a viable cell. The reference further teaches the *in vivo* administration of and antigen and photosensitizing agent (page 6), thus, Claim 37 has been included in the rejection.

Applicant's arguments, filed 5/04/09 have been fully considered but they are not persuasive. Applicant reviews selected parts of the reference, particularly as the reference concerns the internalization of toxic molecules, and argues that this embodiment does not encompass the surface presentation of the toxic molecules.

The reference is clearly not limited to the internalization of toxic molecules, nor to gene therapy nor to *in vitro* internalization, i.e., the exemplified embodiments as Applicant argues. The three methods at pages 7-8 are disclosed only as

"Examples of experimental and clinical utilization". Further, see for example Claim 2 wherein the internalized compounds include, "sugars, proteins, and peptides", none of which are required to be toxic and all of which can be antigens depending on the context. Indeed, at page 2 (as well as in the Abstract) of the reference it is taught that the method is performed, without destroying the functionality of the majority of the cells." After the release of the internalized compound into the cytosol of a live cell processing and presentation on MHC class I would be an inherent property.

It is noted however, that the reference does not teach a method limited to antigen presentation on antigen presenting cells. Thus, the rejection has been withdrawn as it applies to Claims 24-27 and 38.

7. No claim is allowed.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from

7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0878.

10. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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